REMARKS

The Office Action mailed on October 16, 2007 has been received and its contents carefully considered. Paragraphs [0026], [0050], [0051], [0054], and [0055] have been amended to cancel the derivatives specified which the Examiner considers to be new matter. Claims 1-40, 42, and 43 have been amended, new claims 45 and 46 have been added, and claims 41 and 44 have been cancelled.

Applicants are seeking to place at least claims 1-19, 39, 40, and 45 in a condition free of formal and prior art issues so that at least these claims should be allowed. Thus, independent claim 1 has been amended to include the limitations of claim 41. Claims 8-12, 15, 18, and 19 have been amended without prejudice or disclaimer to cancel recitation of the specific derivatives which the Examiner considers new matter, and the previous recitation of "and derivatives thereof" has not been reinstated in these claims. Independent claim 21 has been amended to include the limitations of claim 44. Claims 1-40, 42, and 43 have been amended for formal reasons. Claims 26-30, 33, 36, and 37 have been amended to cancel the specific derivatives which the Examiner considers new matter, and the previous recitation of "and derivatives thereof" has been reinstated in these claims so that Applicants can once again argue that claims reciting the derivatives of the paclitaxel, retinoic acid, and camptothecin are sufficiently definite to satisfy 35 U.S.C. §112. To the best of the undersigned attorney's information and belief, these changes do not introduce any new matter into the Application.

Claims 1-40, 42, 43, 45 and 46 are now pending in the Application. Claims 1 and 21 are written in independent form. For at least the following reasons, it is submitted that this Application is in condition for allowance. Claims 1-19, 39, 40, and 45 in particular are considered to be free of formal and prior art issues so that at least these claims should be allowed.

Separate Record of Interview

Applicants thank the Examiner and his supervisor, Johann Richter, for the telephone interview conducted January 30, 2008. Prior to conducting the interview, a Proposed Amendment was sent via telefax to the Examiner under cover of a sheet listing four issues for discussion. These were discussed in turn.

1. The Examiner considered that the deletions in the specification and claims of the specific derivatives of paclitaxel, retinoic acid, and camptothecin proposed in the Proposed Amendment would resolve the objection to the Amendment filed December 4, 2006, under 35 U.S.C. §132(a) and the rejection of various claims under 35 U.S.C. §112, first paragraph.

2. In the Proposed Amendment, Applicants proposed to reinstate the prior recitation of "and derivatives thereof", or equivalent language, and Counsel presented arguments in support of definiteness of the claims as originally presented. The Examiner indicated that he was not persuaded but would reconsider this issue when presented with written arguments in a formal response.

3. Regarding the rejections in view of Straubiner et al., the Examiner indicated that he found persuasive Applicants' point regarding stability only for low concentrations of taxol shown in Figure 5 of Straubinger et al. and that he would look favorably upon claim 41.

4. Regarding the rejections in view of Scotto et al., no agreement was reached.

I. The objection to the Amendment filed December 4, 2006 under 35 U.S.C. §132(a) is submitted to be resolved by the specification changes made herein. The specification has been amended to cancel the recitation of specific derivatives which the Examiner considers to be new matter. In view of these amendments, Applicants submit that this objection have been resolved and should be withdrawn.

II. The rejection of claims 8-12, 15, 18, 19, 26-30, 33, 36, and 37 under U.S.C. §112, first paragraph, is submitted to be resolved by the claim changes made herein. These claims have been amended to cancel the recitation of specific derivatives which the Examiner considers are not supported verbatim by the original disclosure and are therefore new matter. In view of these amendments, Applicants submit that this rejection is resolved and should be withdrawn.

The Office Action dated August 2, 2006, rejected as unclear and indefinite the claims reciting "and derivatives thereof" regarding the "one or more hydrophobic substances" under U.S.C. §112, first paragraph. The Examiner considered that recitation of a substance, e.g., paclitaxel, and "a derivative thereof" leads to a plethora of compounds, making the scope of the rejected claims unclear (indefinite), i.e., claims 8-18, 21 and 26-37. The Examiner maintained this position during the telephone interview of January 30, 2008.

Accordingly, in order to place at least claims 1-19, 39, 40, and 45 in a condition free of formal and prior art issues so that at least these claims would be allowed, (1) the limitations of claim 41 have been included in independent claim 1 and (2) none of claims 1-19, 39, 40, and 45 include "and derivatives thereof" regarding the specific "one or more hydrophobic substances".

Applicants have amended claims 1-19, 39, 40, and 45 without disclaimer of derivatives of "paclitaxel", "retinoic acid", and "camptothecin", however, since certain of the remaining claims, claims 21-38, 42, and 43, particularly claims 26-36, do contain recitation of "paclitaxel and derivatives of paclitaxel", "retinoic acid and derivatives of retinoic acid", and "camptothecin and derivatives of camptothecin" as included in "one or more hydrophobic substances". It is Applicants' position that claims of the scope of claims 26-36 satisfy U.S.C. §112 because they are clear, sufficiently definite, supported by the Application as-filed, and would enable an artisan to practice the invention.

Applicants therefore respectfully traverse the Examiner's position with respect to "derivatives" in claims 26-36 on the following grounds.

(1) Enabling description - The specification gives specific best mode examples of how to make and use formulated liposomes according to the invention in which the hydrophobic pharmaceutical compounds "paclitaxel", "retinoic acid", and "camptothecin" are incorporated in the liposome (see Example 1-7, 8, and 10, respectively, on pages 14-28 of the Application) so that one of ordinary skill in this art would be readily able to not only practice the invention with these materials but also with known derivatives of these materials which are obtained by conventional chemical manipulation in a routine manner without undue experimentation and which are hydrophobic pharmaceutical compounds as required by the claims. Applicants submit that just because claim language is broad does not mean that it is indefinite, particularly as here regarding well known derivatives of hydrophobic pharmaceutical compounds which themselves meet the criteria of being hydrophobic pharmaceutical compounds. The examples of specific compounds given are submitted to adequately support "derivatives" of these compounds as recited in claims 26-36 and provide reasonable assurance that the hydrophobic derivative compounds embraced by these claims would be useful for the intended purpose.

(2) Operability demonstrated so utility manifest - Indeed, the effectiveness of Applicants' liposomes formulated to incorporate paclitaxel and deliver this drug effectively was demonstrated in tests with mice in Example 10, pages 27 and 28, of the Application. Applicants submit that one of ordinary skill in this art would be readily able therefore to prepare liposomes formulated to incorporate "one or more hydrophobic substances", such as "one or more hydrophobic pharmaceutical compounds", such as "paclitaxel", "retinoic acid", "camptothecin" and their respective derivatives. The Examiner is not seen to have given any statement of record with reasons why the derivatives of these three specific compounds lack the utility asserted.

(3) Claims not unduly broad - Applicants draw the Examiner's attention to the fact that only derivatives of "paclitaxel", "retinoic acid", and "camptothecin" which are "hydrophobic pharmaceutical compounds" are derivatives encompassed by claims 26-

36 so that the "derivatives" language is not considered unduly broad. Applicants' intent to include "derivatives" of "paclitaxel", "retinoic acid", and "camptothecin" in the invention is everywhere manifest in the Application as-filed. The derivative compounds are structurally closely related so that Applicants submit that it is well settled that the supporting disclosure need not be as detailed as when claims cover compounds which are related only in some structural aspect. The scope of the derivatives subject matter embraced by claims 26-36 is therefore submitted to be clear and these claims particularly point out and distinctly claim the subject matter Applicants consider to be their invention. As such, Applicants submit that including "derivatives" in claims 26-36 does not run afoul of 35 U.S.C. §112.

III. The continued rejection of claims 1-9, 18 and 19 under 35 U.S.C. §102(b) as being anticipated by Straubinger et al. (US 5,415,869) is respectfully traversed for claim 1 as amended to include the limitations of claim 41, and the claims depending from claim 1.

The Examiner consider that Straubinger et al. disclose a pharmaceutical formulation comprising at least one taxane present in a pharmaceutically effective amount of 1.5 – 8 mol% and a mixture of one or more negatively charged phospholipids and one or more zwitterions phospholipids in a respective ratio of 1:9 to 3:7 (see claim 1).

Straubinger et al. discloses a pharmaceutical formulation comprising one or more negatively charged phospholipids and one or more zwitterions phospholipids (see claim 1 and examples 2-4 Cols.12 and 13). Straubinger et al.'s formulation remains physically stable for 75 days if it contains a very low content of taxol, such as no more than **2.1%** taxol (see Figure 5 and example 2).

The present invention is distinguishable in that Applicants' formulated lipsomes are able to incorporate a very high content, i.e., **20 mole%,** of one or more hydrophobic

substance, such as the hydrophobic pharmaceutical compound paclitaxel and remain stable for at least 60 days.

Moreover, the present invention does not require a mixture of negatively charged phospholipids and zwitterions phospholipids as does Straubinger et al. In the present invention, both the first and second phospholipids could be negatively charged phospholipids or zwitterions phospholipids.

Accordingly, the disclosure of Straubinger et al. does not disclose (or suggest):

(1)"[O]ne or more hydrophobic substances incorporated in the liposome in an amount of at least 20 mole% to form the formulated liposome, ... wherein the formulated liposome has an incorporation efficiency which remains at at least about 70% of incorporation efficiency for six months or more", as recited in amended claim 1. Applicants' formulated lipsome is able to incorporate a very high content of a drug, such as **20 mole%** paclitaxel, and remain stable for at least 60 days when (2) and (3) below are satisfied.

(2) A phase transition temperature (T_{g1}) of a first phospholipid (about 40°C to 74°C) is larger than the phase transition temperature (T_{g2}) of a second phospholipid (about –30°C and 10°C).

(3) A drug delivery temperature T_1 and a drug storage temperature T_2 chosen at specified ranges such that $T_{g1} > T_1 > T_2 > T_{g2}$.

Thus, Applicants submit that Straubinger et al. fail to teach or suggest a liposome formulation in accordance with Applicants' claimed invention for incorporating a high content of hydrophobic substances therein. As such, it is submitted that Applicants' independent claim 1, and the claims dependent there from, claims 2-9, 18 and 19, are not anticipated by Straubinger et al. so that this ground of rejection should be withdrawn. Moreover, Applicants submit that Straubinger et al. may not be fairly said to suggest the modifications needed to the disclosure of Straubinger et al. which would be needed to meet Applicants claims. For this reason Applicants submit that the

disclosure of Straubinger et al. does not set out a *prima facie* case of obviousness against claim 1 and the claims depending therefrom.

IV. The continued rejection claims 1-7, 19, 21-25 and 37 under 35 U.S.C. §102(b) as being anticipated by Scotto et al. (US 4,873,089) is respectfully traversed.

Scotto et al. disclose a process for the preparation of fusogenic proteolipsomes. Scotto et al. discloses some phospholipids in column 5, lines 37-64, but Scotto et al.'s formulation is used for incorporating proteins and is not directly used for incorporating hydrophobic substances. The Examiner acknowledges that Scotto et al. do not teach the hydrophobic substances paclitaxel, retinoic acid, and camptothecin being encapsulated in their liposome formulations.

The present invention is distinguishable in that Applicants' formulated liposomes directly incorporate one or more hydrophobic substances. Applicants submit that the "fusogens" of Scotto et al. are not hydrophobic substances within Applicants' claims. For example, claim 4 of Scotto recites, "wherein said fusogen is a fatty acid, sterol, or phospohlipid which when included in a phospholipid bilayer renders the bilayer capable of fusion with integral membrane proteins ..." These are well-know amphiphilic, membrane-forming materials and are readily incorporated in the liposome without any stability issues. In contrast, the hydrophobic substances of the present invention are not considered to be membrane-forming materials and even destabilize a liposome formulation when incorporated therein in high amounts.

Thus, Applicants submit that the disclosure of Scotto et al. does not disclose (or suggest):

(1)"[O]ne or more hydrophobic substances incorporated in the liposome in an amount of at least 20 mole% to form the formulated liposome, ... wherein the formulated liposome has an incorporation efficiency which remains at at least about 70% of incorporation efficiency for six months or more", as recited in amended claims 1

and 21. Applicants' formulated lipsome is able to incorporate a very high content of a drug, such as **20 mole%** paclitaxel, and remain stable for at least 60 days when (2) and (3) below are satisfied.

(2) A phase transition temperature (T_{g1}) of a first phospholipid (about 40°C to 74°C) is larger than the phase transition temperature (T_{g2}) of a second phospholipid (about –30°C and 10°C).

(3) A drug delivery temperature T_1 and a drug storage temperature T_2 chosen at specified ranges such that $T_{g1} > T_1 > T_2 > T_{g2}$.

In view of these distinctions, Applicants respectfully submit that Scotto et al. fail to teach or suggest a formulated liposome in accordance with Applicants' claimed invention for incorporating a high content of hydrophobic substances therein. As such, it is submitted that Applicants' independent claim 1, and the claims dependent there from, claims 2-7 and 19, and independent claim 21, and the claims depending there from, claims 22-25 and 37, are not anticipated by Scotto et al. so that this ground of rejection should be withdrawn. Moreover, Applicants submit that Scotto et al. may not be fairly said to suggest the modifications needed to the disclosure of Scotto et al. which would be needed to meet Applicants claims as amended. For this reason Applicants submit that the disclosure of Scotto et al. does not set out a *prima facie* case of obviousness.

V. The rejection of claim 41 under 35 U.S.C. §103(a) as being unpatentably obvious over Straubinger et al. (US 5,415,869) in view of Rahman (US 5,424,073) is moot in view of cancellation of this claim.

VI. The rejection of claims 20 and 38 under 35 U.S.C. § 103(a) as being unpatentably obvious over Scotto et al. (US 4,873,089) in view of Crosasso et al. (J. Controlled Release ...) is respectfully traversed.

The Examiner acknowledges that Scotto et al. do not teach the addition of MPEG-DSPE with the liposome formulations. The Examiner therefore relies on Crosasso et al. because it is know in the art that PEGylated liposomes have a longer circulation time in the blood stream prior to being metabolized as taught by Crosasso et al. (page 20, 2nd Col., lines 6-24.

Claim 20 depends from claim 1 and claim 38 depends from claim 21, and these claims are patentable for the same reasons given above regarding claims 1 and 21. Applicants repeat the distinctions presented above regarding Scotto et al. Moreover, Applicants submit that the disclosure of Crosasso et al. does not teach (2) and (3), and may or may not teach (3) so that the combined disclosures of Scotto et al. and Crosasso et al. are not seen to meet Applicants' claims 20 and 38 so that no *prima facie* case of obviousness has been made out and this ground of rejection should be withdrawn.

VII. The rejection of claims 8-18, and 26-36 under 35 U.S.C. § 103(a) as being unpatentably obvious over Scotto et al. (US 4,873,089) in view of Unger et al. (US 5,733,572) and Castor et al. (US 5,776,486) is respectfully traversed.

The Examiner acknowledges that Scotto et al. do not teach the hydrophobic substances paclitaxel, retinoic acid, and camptothecin being encapsulated in their liposome formulations. The Examiner therefore relies on Castor et al., Col. 1, lines 33-36, for the teaching that liposome-based drug formulations are able to achieve the equivalent therapeutic efficacy of the free drug. Castor et al. additionally teach encapsulation of paxlitaxel or camptothecon with liposomes comprising EPC and cholesterol. Because of the toxicity associated with free paclitaxel, retinoic acid, and camptothecin, the Examiner considers that it would be beneficial to incorporate these drugs into the liposome formulations of Scotto et al. The Examiner additionally relies on Unger et al. as teaching DPPC liposomes incorporating vitamin A (retinoic acid) , (see Example 8, Col. 53, lines 6-15). The Examiner acknowledges that Unger et al. do

not teach first and second phospholipids, or selection of same based on phase transition temperatures.

Claims 8-16 depend from claim 1 and claims 26-36 depends from claim 21 and these claims are patentable for the same reasons given above regarding claims 1 and 21. Applicants repeat the distinctions presented above regarding Scotto et al. Moreover, Applicants submit that the disclosure of Crosasso et al. and Unger et al. do not teach (2) and (3), and may or may not teach (1). In any event, Applicants submit that the combined disclosures of Scotto et al., Unger et al., and Crosasso et al. are not seen to meet Applicants' claims 8-16 and 26-38 so that no *prima facie* case of obviousness has been made out and this ground of rejection should be withdrawn.

VIII. The rejection of claims 42-44 under 35 U.S.C. § 103(a) as being unpatentably obvious over Scotto et al. (US 4,873,089) in view of Unger et al. (US 5,733,572) and Castor et al. (US 5,776,486), and further in view of Rahman (US 5,424,073) is moot regarding cancelled claim 44 and is respectfully traversed for claims 42 and 43.

The Examiner acknowledges that Scotto et al. in view of Unger et al. and Castor et al. do not teach the hydrophobic substances paclitaxel, retinoic acid, and campotothecin present in a liposomal formulation in an amount or 3-25 mol%, or at least 20 mol% as instantly claimed in claim 21 as amended to include the limitations of claim 44. The Examiner therefore relies on Rahman, Col. 3, lines 24-54, and examples 1-4, for this teaching.

Applicants repeat distinctions (1) – (3) above regarding Scotto et al. and submit that the disclosures of Crosasso et al. and Unger et al. do not teach (1) – (3), and that the disclosure of Rahman is not considered to teach (2) and (3). Thus, Applicants submit that the combined disclosures of Scotto et al., Unger et al., Crosasso et al., and Rahman are not seen to meet Applicants' claims 42 and 43 so that no *prima facie* case of obviousness has been made out and this ground of rejection should be withdrawn.

CONCLUSIONS

In view of the foregoing amendments and arguments, it is submitted that claims 1-40, 42, 43, 45 and 46, and the Application are in condition for allowance. Such action and the passing of this case to issue are requested.

Should the Examiner consider that a conference would help to expedite the prosecution of this Application, the Examiner is hereby invited to contact the undersigned counsel to arrange for such an interview.

REQUEST FOR EXTENSION OF TIME

Applicants request a first extension of time for responding to the Office Action dated October 16, 2007. A first extension fee in the amount of $120.00 is now due. This fee is submitted herewith in the attached credit card form PTO-2038. Should the remittance be accidentally missing or insufficient, the Commissioner is hereby authorized to charge the fee to our Deposit Account No. 18-0002 and is requested to advise us accordingly.

Respectfully submitted,

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